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Examiner	:	Brian Yong S. Kwon
Art Unit	:	1614
Applicant	:	Roger L. Papke
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DECLARATION OF ROGER L. PAPKE, Ph.D., UNDER 37 C.F.R. ə 1.132

Sir:

I, Roger L. Papke, Ph.D., of the University of Florida, Department of Pharmacology and Therapeutics, hereby declare:

THAT, I am the named inventor on the above-referenced patent application;

THAT, I have received the following degrees:

Ph.D. Neurobiology and Behavior	1987	Cornell University, Ithaca, NY
M.S. Physiology	1976	New York University, NY, NY
B.A. Biology and Classics	1975	New York University, NY, NY

THAT, I have been employed professionally as follows:

1987	Postdoctoral Research Associate: Department of Pharmacology, Cornell University
1987	Lecturer: Department of Neurobiology and Behavior, Cornell University
1988-1993	Postdoctoral Research Fellow: Molecular Neurobiology Laboratory, Salk Institute

1993-1998	Assistant Professor: Department of Pharmacology and Therapeutics, University of Florida
1994-1998	Affiliate Assistant Professor: Department of Neuroscience University of Florida
1998-present	Associate Professor: Department of Pharmacology and Therapeutics, University of Florida
1998-present	Affiliate Associate Professor: Department of Neuroscience University of Florida

THAT, I have published extensively in my field and some of the publications are as follows:

1. Roger L. Papke and Robert E. Oswald. 1986. Effects of allosteric ligands on the gating of single channel currents in bc3h-1 cells. N.A.T.O. *Advanced Research Workshop Mechanism of Action of The Nicotinic Acetylcholine Receptor,* Santorini, Greece. NATO ASI Series Vol. H3 Ed. A. Maelicke Springer-Verlag, Berlin.

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9. Michael M. Francis, and Roger L. Papke, 2000. The functional diversity of nicotinic receptors in the nervous system: perspectives on receptor subtypes and receptor specialization *Handbook of Experimental Pharmacology* **144**: 301-336.

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12. Roger L. Papke and Julia K. Porter Papke. 2002. The Use of Net-Charge Analysis for the Study of Ion Channel Pharmacology. *Axobits* November 2002 **36**:6-9

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16. Robert E. Oswald, Roger L. Papke and Ronald J. Lukas. 1989. Characterization of nicotinic acetylcholine receptor channels of the TE671 human medulloblastoma cell line. *Neuroscience letters*. **96**:207-212.

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111. C.J. Frazier, and R.L. Papke 2003. Activation Of α7 Nicotinic Receptors Can Contribute To Induction Of A Muscarinic Afterdepolarization In Dentate Mossy Cells. *33rd Annual Meeting of the Society for Neuroscience*

112. A.N. Placzek, E. M. Meyer, T.A.S. Papke, & R.L. Papke. 2003. A single residue in the α7 nicotinic acetylcholine receptor tm2 domain is required for potentiation by 5-hydroxyindole. *33rd Annual Meeting of the Society for Neuroscience*

113. J. Dominy, J. Thinschmidt, J. Peris, R. Dawson, R. L. Papke 2003. An Apparent Dissociation Between Intracellular Taurine Content and Long-Lasting Potentiation in the Rat Hippocampus *33rd Annual Meeting of the Society for Neuroscience*

THAT, through my years of research, I have kept up to date on the technical literature and maintained contact with experts in the field by participating in professional meetings and seminars, and by direct personal contact. As a result, I am familiar with the general level of skill of those working in the fields of molecular biology and pharmacology, and particularly as they relate to nicotinic acetylcholine receptors;

THAT, I have read and understood the specification and claims of the subject application and the Office Action dated August 26, 2003;

AND, being thus duly qualified, do further declare:

The Office Action indicates that because the Crooks *et al.* patent teaches the administration of metanicotine to treat Alzheimer's disease (AD) and the Newhouse *et al.* publication teaches the administration of ABT-418 to treat AD, it would have been obvious to combine the two therapies to treat AD.

Numerous nicotinic agonists, including nicotine itself, GTS-21, metanicotine (TC-2403), ABT-418, ABT-089 and SIB-1553A have been proposed as therapeutic agents for CNS indications, such as AD, Parkinson's disease, pain, and schizophrenia. All of these compounds have been characterized as agonists or partial agonists for select nAChR subtypes. Additionally, all of the aforementioned compounds, with the exception of metanicotine, produce varying amounts of residual inhibition (or protracted desensitization), making them in fact mixed agonists-antagonists, as described in paragraphs 0026 and 0027 of the specification. My laboratory has previously shown that metanicotine selectively activates the high affinity alpha4beta2 nAChR subtype with little agonist activity on the alpha7 subtype (Papke RL, *et al.*, "The activation and inhibition of human nicotinic acetylcholine receptor by RJR-2403 indicate a selectivity for the alpha4beta2 receptor subtype" *J. Neurochem.*, 75(1):204-16, July 2000). Although metanicotine was once proposed to be

a potential drug for the treatment of AD (as indicated in the Crooks *et al.* patent), recent studies have suggested that the appropriate molecular target for this indication is in fact the alpha7 receptor (Kem WR "The brain alpha7 nicotinic receptor may be an important therapeutic target for the treatment of Alzheimer's disease: studies with DMXBA (GTS-21)" *Behav. Brain. Res.*, 113(1-2):169-81, August 2000), which metanicotine does not effectively stimulate. Thus, based upon what was known of metanicotine's activity from the scientific literature at the time the subject patent application was filed, there would be no reason to administer metanicotine to treat AD. The compounds ABT-418 and GTS-21 do activate alpha7 receptors, with profiles of activity that are non-selective for alpha7 and selective for alpha7, respectively. However, while the activity on alpha7 receptors makes ABT-418 and GTS-21 candidate drugs for AD, their usefulness would be limited by their residual antagonist activity, which restricts their effectiveness on alpha7 receptors and potentially would compromise other functions mediated by non-alpha7 receptors in the brain and peripheral nervous system.

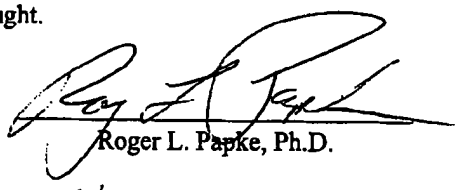
The data in the subject patent application shows that the combination of metanicotine with compounds that are nAChR antagonists or mixed agonists-antagonists, such as ABT-418 and GTS-21, likely have a synergistic (*i.e.*, far more than additive) effect through the ability of metanicotine to diminish the otherwise concomitant antagonist activity of the other cholinergic antagonist or mixed agonist-antagonist. As demonstrated in Example 5 and Figures 6A and 6B of the subject patent application and the Papke (2002) publication (*J. Pharmacol. Exp. Ther.*, 301(2):765-773, 2002), which is submitted herewith, only co-application of metanicotine was effective at decreasing residual inhibition by mixed agonists-antagonists and protecting receptor function. This effect was not observed by the other agents tested (the local anesthetics QX-314 and tetracaine). Moreover, this ability of metanicotine to protect nAChR function from long-term inhibition by antagonists or mixed agonists-antagonists was not previously recognized in the scientific literature, and would not have been expected based upon the individual activities of metanicotine and the other compounds.

As indicated in paragraph 0014 of the subject patent application, the fact that metanicotine can protect nicotinic receptors from the inhibitory after-effects of other potentially therapeutic compounds is of great clinical significance. Co-administration of metanicotine with other

compounds can provide a means to tune a spectrum of effects to enhance receptor subtype-selective activation, thereby providing a more positive profile of effects.

The undersigned declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or of any patent issuing thereon.

Further declarant sayeth naught.

Signed: 

Roger L. Papke, Ph.D.

Date: Nov. 25, 2003